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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN DERIVATIVE

(57) Abstract

A pharmaceutical composition containing ([3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin) as an active ingredient. The composition is formulated as a microemulsion or microemulsion preconcentrate using a carrier medium comprising a hydrophilic phase; a transesterified ethoxylated vegetable oil; and a surfactant. The composition has good stability and bio-pharmaceutical properties and is useful in the treatment of multiple drug resistance syndrome in humans.

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Pharmaceutical Composition containing Cyclosporin Derivative

This invention relates to a pharmaceutical formulation having as the active ingredient a cyclosporin derivative that is useful in the treatment of multiple drug resistance syndrome. In particular this invention relates to a pharmaceutical formulation that contains ([3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin) as an active ingredient.

The resistance of tumour cells to chemotherapeutics is a major cause in the failure of chemotherapy. One form of resistance to chemotherapeutics is "multiple drug resistance" where the tumour cells become cross-resistant to a variety of chemotherapeutics; for example alkaloids, anthracyclines, actinomycin D, adriamycin and colchicine. Multiple drug resistance syndrome has been correlated in many reports with the overexpression of the transmembrane glycoproteins called P-glycoproteins (Pgp). Cyclosporins have been found to reverse multiple drug resistance syndrome and [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin in particular has been found to be effective. [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin and its utility is described in detail in European patent publication No 296 122.

The cyclosporins comprise a class of structurally distinctive, cyclic, poly-N-methylated undecapeptides, generally possessing pharmacological, in particular immunosuppressive, anti-inflammatory and/or anti-parasitic activity, each to a greater or lesser degree. Cyclosporins are generally very insoluble in aqueous media. Consequently, difficulties have arisen in developing pharmaceutically acceptable carriers which allow delivery of the drug in sufficiently high concentrations to permit convenient use and which allow efficient and consistent absorption of the drug by the body. Also specific cyclosporins present very specific problems in relation to their administration and, in particular, in providing galenic formulations. Species specific problems also arise with regard to drug bioavailability and variability in patient dose response. This also applies to the compound ([3'-desoxy-3'-oxo- MeBmt]¹-[Val]²-Ciclosporin) which presents very specific problems in relation to providing galenic formulations containing it.

To deal with the general problems of formulating cyclosporins, British patent application 2 222 770 A discloses galenic formulations, containing cyclosporins, that are in the form of microemulsions or microemulsion preconcentrates. These formulations comprise a hydrophilic phase, a lipophilic phase and a surfactant. The 5 following components for the hydrophilic phase are given: Transcutol, Glycofurool and 1,2-propylene glycol. Medium chain fatty acid triglycerides are disclosed as being suitable for the lipophilic phase. Reaction products of natural or hydrogenated vegetable oils and ethylene glycol are given as surfactants. However this British patent application did not deal with the problems of formulating 10 ($[3'$ -desoxy- $3'$ -oxo-MeBmt] 1 -[Val] 2 - Ciclosporin) which is much more lipophilic than most other cyclosporins.

It has now been surprisingly found that stable formulations containing ($[3'$ -desoxy- $3'$ -oxo-MeBmt] 1 -[Val] 2 -Ciclosporin) that have good bioavailability and good inter-subject variability characteristics can be obtained.

15 Accordingly this invention provides a pharmaceutical composition that comprises ($[3'$ -desoxy- $3'$ -oxo- MeBmt] 1 -[Val] 2 -Ciclosporin) as an active ingredient and a carrier medium comprising (1) a hydrophilic phase; (2) a transesterified ethoxylated vegetable oil; and (3) a surfactant. Preferably the formulation is in the form of a microemulsion or microemulsion preconcentrate.

20 This composition provides a surprisingly high bioavailability (about twice that of a conventional Ciclosporin formulation) and hence the dosage of ($[3'$ -desoxy- $3'$ -oxo- MeBmt] 1 -[Val] 2 -Ciclosporin) required to be delivered can be decreased. The composition is also convenient to use and permits efficient and consistent absorption of ($[3'$ -desoxy- $3'$ -oxo- MeBmt] 1 -[Val] 2 -Ciclosporin) by the 25 body. The composition is particularly effective in treating multiple drug resistance syndrome in, for example, cancer patients undergoing chemotherapy.

30 Preferably the composition is in the form of a "microemulsion preconcentrate", in particular of the type providing o/w (oil-in-water) microemulsions. However the composition may be in the form of a microemulsion which additionally contains an aqueous phase; preferably water.

A "microemulsion preconcentrate" is defined in this specification as being a formulation which spontaneously forms a microemulsion in an aqueous medium, for example, in water or in the gastric juices after oral application. The formation of such a microemulsion is highly desirable to overcome the problems discussed above.

5 A "microemulsion" is a non-opaque or substantially non-opaque colloidal dispersion that is formed spontaneously or substantially spontaneously when its components are brought into contact. A microemulsion is thermodynamically stable and contains dispersed particles of a size less than about 2000 Å. Generally microemulsions comprise droplets or particles having a diameter of less than about 10 1500 Å; typically from 100 to 1000 Å. Further characteristic can be found in British patent application 2 222 770 A; the disclosure of which is incorporated by reference.

10 A "pharmaceutical composition" means a composition in which the individual components or ingredients are themselves pharmaceutically acceptable and, when a particular form of administration is foreseen, are suitable or acceptable for that form 15 of administration.

The transesterified ethoxylated vegetable oil may comprise 10 to 85 % by weight of the carrier medium; preferably 15 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably about 20 % by weight.

20 The surfactant may comprise 5 to 80 % by weight of the carrier medium; preferably 10 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably about 60 % by weight.

The hydrophilic phase may comprise 10 to 50 % by weight of the carrier medium; preferably 15 to 40 % by weight, more preferably 20 to 30 % by weight and even more preferably about 20 % by weight.

25 The hydrophilic phase may be selected from Transcutol (which has the formula $C_2H_5-[O-(CH_2)_2]_2-OH$), Glycofurool (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether) and 1,2-propylene glycol, or mixtures thereof, and is preferably 1,2-propylene glycol. The hydrophilic phase may include further hydrophilic co-components, for example ethanol. These co-components will generally be present in partial replacement of other components of the hydrophilic 30 phase. While the use of ethanol in the compositions is not essential, it has been

found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are improved, in particular the risk of cyclosporin precipitation following encapsulation procedures is reduced. Thus the shelf life stability may be extended by employing 5 ethanol or some other such co-component as an additional ingredient of the hydrophilic phase. The ethanol may comprises 0 to 60 % by weight of the hydrophilic phase; preferably 20 to 55% by weight and more preferably about 55 % by weight.

The active ingredient is preferably present in an amount of 5 to 15 % by 10 weight of the composition; more preferably about 10 %.

Suitable transesterified ethoxylated vegetable oils may be obtained by reacting various natural vegetable oils (for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil, or mixtures thereof) with polyethylene glycols that have an average molecular weight of from 15 200 to 800, in the presence of an appropriate catalyst. These procedures are known and an example is described in US Patent 3 288 824. Transesterified ethoxylated corn oil is particularly preferred.

Transesterified ethoxylated vegetable oils are known and are commercially available under the trade name Labrafil (see H. Fiedler, Lexikon der Hilfsstoffe, 3rd 20 edition, vol 2, page 707). Examples are Labrafil M 2125 CS (obtained from corn oil and having an acid number of less than about 2, a saponification number of 155 to 175, an HLB value of 3 to 4, and an iodine number of 90 to 110), and Labrafil M 1944 CS (obtained from kernel oil and having an acid number of about 2, a saponification number of 145 to 175 and an iodine number of 60 to 90). Labrafil M 25 2130 CS (which is a transesterification product of a C₁₂₋₁₈ glyceride and polyethylene glycol and which has a melting point of about 35 to 40°C, an acid number of less than about 2, a saponification number of 185 to 200 and an iodine number of less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is Labrafil M 2125 CS which can be obtained, for example, from Gattefossé, 30 Saint-Priest Cedex, France.

The surfactant may comprise reaction products of a natural or hydrogenated castor oil and ethylene oxide. The natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various such 5 surfactants are commercially available. The polyethyleneglycol-hydrogenated castor oils available under the trade name Cremophor are especially suitable. Particularly suitable are Cremophor RH 40, which has a saponification number of about 50 to 60, an acid number less than about 1, a water content (Fischer) less than about 2%, an n_D^{60} of about 1.453 to 1.457 and an HLB of about 14 to 16; Cremophor RH 60, 10 which has a saponification number of about 40 to 50, an acid number less than about 1, an iodine number of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an n_D^{25} of about 1.453 to 1.457 and an HLB of about 15 to 17; and Cremophor EL, which has a molecular weight (by steam osmometry) of about 1630, 15 a saponification number of about 65 to 70, an acid number of about 2, an iodine number of about 28 to 32 and an n_D^{25} of about 1.471.

Similar or identical products which may also be used are available under the trade names Nikkol (e.g. Nikkol HCO-40 and HCO-60), Mapeg (e.g. Mapeg CO-40h), Incrocas (e.g. Incrocas 40), and Tagat (e.g. Tagat RH 40). These surfactants are further described in Fiedler loc. cit.

20 The surfactant may also be selected from polyoxyethylene sorbitan fatty acid esters, such as mono- and tri-lauryl, palmityl, stearyl and oleyl esters. Examples of commercially available esters are those available under the trade name Tween (see Fiedler, pages 1300 to 1304) and particularly Tween 60 (polyoxyethylene(20) sorbitan mono stearate) and Tween 80 (polyoxyethylene(20) sorbitan mono oleate).

25 Preferably the surfactant is Cremophor RH 40.

The compositions may also include further additives or ingredients, for example antioxidants (such as ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT) and tocopherols) and/or preserving agents. These additives or ingredients may comprise about 0.05 to 1% by weight of the total weight 30 of the composition. The compositions may also include sweetening or flavoring agents in an amount of up to about 2.5 or 5% by weight based on the total weight of

the composition. Preferably the antioxidant is α -tocopherol (vitamin E).

The compositions exhibit especially advantageous properties when administered orally; for example in terms of consistency and high level of bioavailability obtained in standard bioavailability trials. These trials are performed in healthy patients using a nonspecific monoclonal kit to determine the level of $[(3'\text{-desoxy-}3'\text{-oxo-MeBmt})^1\text{-[Val]}^2\text{-Ciclosporin}]$. Results have shown that at least 170% greater bioavailability can be obtained in mammals and about 200% in humans (as compared to the commercially available, oral Ciclosporin formulation). This means that the dosage to be delivered can be reduced as compared to the commercial oral form. The compositions also provide less food interaction, which has been observed with the commercially available oral form of Ciclosporin; especially with fat rich food. Moreover, inter-subject and intra-subject variability of pharmacokinetic parameters may be significantly lower with the compositions than with the commercial oral form of Ciclosporin. Specifically the difference between the pharmacokinetic parameters with food intake and without food intake, or even between day time absorption and night time absorption, may be reduced.

Thus pharmacokinetic parameters, for example absorption and blood levels, become surprisingly more predictable and problems in administration with erratic absorption may be eliminated or reduced. Additionally the composition is compatible with tenside materials, for example bile salts, present in the gastro-intestinal tract. That is, the composition is fully dispersible in aqueous systems comprising such natural tensides and is thus capable of providing microemulsion systems in situ which are stable and do not exhibit precipitation of the active ingredient or other disruption of fine particulate structure. The function of the composition upon oral administration remains substantially independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual.

The compositions are preferably compounded in unit dosage form, for example by filling them into orally administrable capsule shells. The capsule shells may be soft or hard gelatine capsule shells. Where compositions are in unit dosage form, each unit dosage will suitably contain between 10 and 200 mg $[(3'\text{-desoxy-}3'\text{-oxo-MeBmt})^1\text{-[Val]}^2\text{- Ciclosporin}]$, more preferably between 10 and 150

mg; for example 15, 20, 25, 50 or 100 mg [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the phase of therapy and the like.

5 However, if desired, the composition may be in drink solution form and may include water or any other aqueous system, to provide microemulsion systems suitable for drinking.

10 The utility of the compositions can be observed in standard clinical tests such as those disclosed in EP 296 122 using dosages in the range of 200 mg to 1800 mg per day for a 75 kilogram adult and in standard animal models. The increased 15 bioavailability of the active ingredient provided by the compositions can be observed in standard animal tests such as described in example 13 and in clinical trials.

15 The optimal dosage to be administered to a particular patient must be considered carefully by the treating physician as individual response to and metabolism of [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin may vary. It may be advisable to monitor the blood serum levels of the cyclosporin by radioimmunoassay, monoclonal antibody assay, or other appropriate conventional means. Dosages of 20 [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin for treatment of multiple drug resistance syndrome will generally range from 200 mg to 1800 mg per day for a 75 kilogram adult, preferably 300 mg to 1500 mg, with the optimal dosage being approximately 500 mg per day. Satisfactory results are obtained by administering 25 about 500 mg per day in the form of five capsules each containing 100 mg or ten capsules each containing 50 mg.

25 In a further aspect the invention also provides a process for the production of a pharmaceutical composition as defined above, which process comprises bringing (1) a hydrophilic phase; (2) a transesterified ethoxylated vegetable oil; and (3) a surfactant into intimate admixture in relative proportions of components (1), (2) and (3) and adding the active ingredient. When required the composition may be compounded into unit dosage form, for example filling the composition into gelatine 30 capsules.

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Optionally further components or additives, in particular a hydrophilic phase co-component, for example ethanol, may be mixed with components (1), (2) and (3) or with or after addition of the active ingredient.

5 The composition may be combined with sufficient water or sufficient of an aqueous solvent medium such that a microemulsion is obtained.

Embodiments of the invention are now described, by way of example only, with reference to the drawings in which:

10 Figure 1 shows a three way plot of the range of concentrations of preferred components of the carrier medium which result in microemulsion preconcentrates with the concentration of the active ingredient remaining constant at 10% and that of ethanol at 15%. Formulations within the shaded area form microemulsions spontaneously in aqueous media. Formulations outside of the shaded area form other disperse systems, e.g., emulsions, in aqueous media.

The following examples illustrate some preferred forms of the invention.

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Table 1: Examples 1 to 4

Ingredients/Example	1	2	3	4
Active Ingredient	100 mg	100 mg	100 mg	100 mg
Ethanol absolute	105 mg	150 mg	100 mg	150 mg
Labrafil M 2125 CS	150 mg	150 mg	640 mg	150 mg
1,2-polypropylene	95 mg	75 mg	80 mg	150 mg
Cremophor RH 40	525 mg	525 mg	80 mg	450 mg
α -tocopherol	1 mg	1 mg	1 mg	1 mg
Tween 80	-	-	-	-
Total	1001 mg	1001 mg	1001 mg	1001 mg

Table 2: Examples 5 to 8

Ingredients/Example	5	6	7	8
Active Ingredient	100 mg	100 mg	100 mg	100 mg
Ethanol absolute	100 mg	100 mg	100 mg	100 mg
Labrafil M 2125 CS	160 mg	240 mg	160 mg	320 mg
1,2-polypropylene	80 mg	80 mg	160 mg	80 mg
Cremophor RH 40	560 mg	480 mg	480 mg	400 mg
α -tocopherol	1 mg	1 mg	1 mg	1 mg
Tween 80	-	-	-	-
Total	1001 mg	1001 mg	1001 mg	1001 mg

Table 3: Examples 9 to 12

Ingredients/Example	9	10	11	12
Active Ingredient	100 mg	100 mg	100 mg	100 mg
Ethanol absolute	100 mg	100 mg	100 mg	100 mg
Labrafil M 2125 CS	160 mg	240 mg	480 mg	560 mg
1,2-polypropylene	160 mg	160 mg	160 mg	80 mg
Cremophor RH 40	-	-	-	-
α -tocopherol	1 mg	1 mg	1 mg	1 mg
Tween 80	480 mg	400 mg	160 mg	80 mg
Total	1001 mg	1001 mg	1001 mg	1001 mg

To produce the compositions, the Labrafil M 2125 CS, the Cremophor RH 40 (or Tween) and the polypropylene glycol are mixed thoroughly and then deaerated. The [3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin is then suspended in the mixture and the mixture again deaerated. The ethanol is then added to the mixture. It may be necessary to warm the PEG-hydrogenated castor oil slightly (e.g. to about 30°C) until it melts to a clear liquid. The composition obtained is suitable for oral administration as a drink solution or in a soft gelatin capsule containing a measured quantity, for example 1 ml, of the composition. The compositions are filled into the capsules and sealed using, for example, the Quali-Seal technique.

20 Stability

The capsules are packaged in doubled sided aluminium blisters and stored at 5°C, 25°C (at 50% humidity) and 30°C (at 65 % humidity). The capsules are examined after 6 months and 12 months. No change in the appearance of the

contents and the capsule shells is observed. The capsules are therefore very stable.

EXAMPLE 13: Bioavailability in dogs

The biopharmaceutical properties of the composition of Example 1 is compared with the marketed soft-gelatine capsule of Ciclosporin. The forms are compared after oral administration to 7 male beagle dogs in a cross-over design. The pharmacokinetic profile of the active ingredient was determined in whole blood over 24 hours. The areas under the curve of the blood concentration versus time curves (AUC), C_{max} and T_{max} are determined. Doses of 50 mg or 350 mg of active ingredient are used; 2 dogs for 50 mg and 5 dogs for 350 mg.

10 Composition X (commercial form, soft gelatin capsule) composition:

Ciclosporin	11 % by weight
Labrafil	32 % by weight
ethanol	11 % by weight
Maize oil	46 % by weight

15 Drug administration:

7 male beagle dogs weighing around 12 kg are used in the trial. Twenty hours before drug administration, food is withdrawn but the animals are allowed free access to water until the beginning of the experiment. The dosage forms are administered by gavage to the animals, early in the morning (approx. 8.00 am), followed by 20 ml NaCl 0.9% solution. Three hours after the administration, the animals are again allowed free access to water and food. A wash-out period of a week is necessary between 2 administrations to the same animal.

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Blood sampling:

Blood samples of 2 ml (or 5 ml for the blank sample) are taken from the venae cephalica (forearm) using a sterile needle (diameter about 1.2 mm) and collected into 5 ml plastic tubes containing EDTA. The samples are taken before administration of the drug and at 15 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours and 24 hours after the oral administration of the drug. The blood samples are stored at about -20°C until the drug assay is carried out. The blood samples are analysed by nonspecific radioimmunoassay (RA). The areas under the blood drug concentration versus time curves (AUC) are calculated using the trapezoidal rule. An analysis (CV) of variance is performed and the mean AUCs, Cmax and Tmax are compared statistically by the Tukey test. The results obtained are shown in the following table.

Table 4: AUC, Cmax and Tmax results in dog

Example	Dose (mg)	AUC (0 - 24hr)	Cmax (ng/ml)	Tmax (hrs)
X	350	10851	1299	2.00
X	50	1926	477	1.25
1	350	18040	2092	1.80
1	50	4139	602	1.25

Conclusion: The composition of Example 1 has a significantly higher bioavailability (factor 1.7 at a dosage of 350 mg and factor 2.1 at a dosage of 50 mg) than the commercial, soft-gelatin capsule of Ciclosporin.

CLAIMS

1. A pharmaceutical composition that comprises ([3'-desoxy-3'-oxo-MeBmt]¹-[Val]²-Ciclosporin) as an active ingredient and a carrier medium comprising (1) a hydrophilic phase; (2) a transesterified ethoxylated vegetable oil; and (3) a surfactant.
- 5
2. A composition according to claim 1 in the form of a microemulsion preconcentrate of the type providing o/w (oil-in-water) microemulsions.
- 10
3. A pharmaceutical composition according to claim 1 in which the transesterified ethoxylated vegetable oil comprises 10 to 85 % by weight of the carrier medium; the surfactant comprises 5 to 80 % by weight of the carrier medium; and the hydrophilic phase comprises 10 to 50 % by weight of the carrier medium.
- 15
4. A pharmaceutical composition according to claim 3 in which the transesterified ethoxylated vegetable oil comprises 15 to 70 % by weight of the carrier medium; the surfactant comprises 10 to 70 % by weight of the carrier medium; and the hydrophilic phase comprises 15 to 40 % by weight of the carrier medium.
- 20
5. A pharmaceutical composition according to claim 4 in which the transesterified ethoxylated vegetable oil comprises about 20 % by weight of the carrier medium; the surfactant comprises about 60 % by weight of the carrier medium; and the hydrophilic phase comprises 20 % by weight of the carrier medium.
6. A pharmaceutical composition according to claim 1 in which the hydrophilic phase includes a component selected from Transcutol, Glycofurool and 1,2-propylene glycol, or mixtures thereof.
- 25
7. A pharmaceutical composition according to claim 6 in which the hydrophilic phase includes ethanol as a further hydrophilic co-component.

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8. A pharmaceutical composition according to claim 7 in which the ethanol comprises 0 to 60 % by weight of the hydrophilic phase.

9. A pharmaceutical composition according to claim 1 in which the active ingredient is present in an amount of 5 to 15 % by weight of the composition.

5 10. A pharmaceutical composition according to claim 1 in which the transesterified ethoxylated vegetable oil is a transesterified ethoxylated corn oil.

10 11. A pharmaceutical composition according to claim 1 in which the surfactant is a reaction product of a natural or hydrogenated castor oil and ethylene oxide, or is a polyoxyethylene sorbitan fatty acid ester.

12. A pharmaceutical composition according to claim 1 for use in the treatment of multiple drug resistance syndrome in humans.

15 13. A process for the production of a pharmaceutical composition as defined in claim 1, which process comprises mixing together proportions of the hydrophilic phase, the transesterified ethoxylated vegetable oil, and the surfactant and adding the active ingredient.

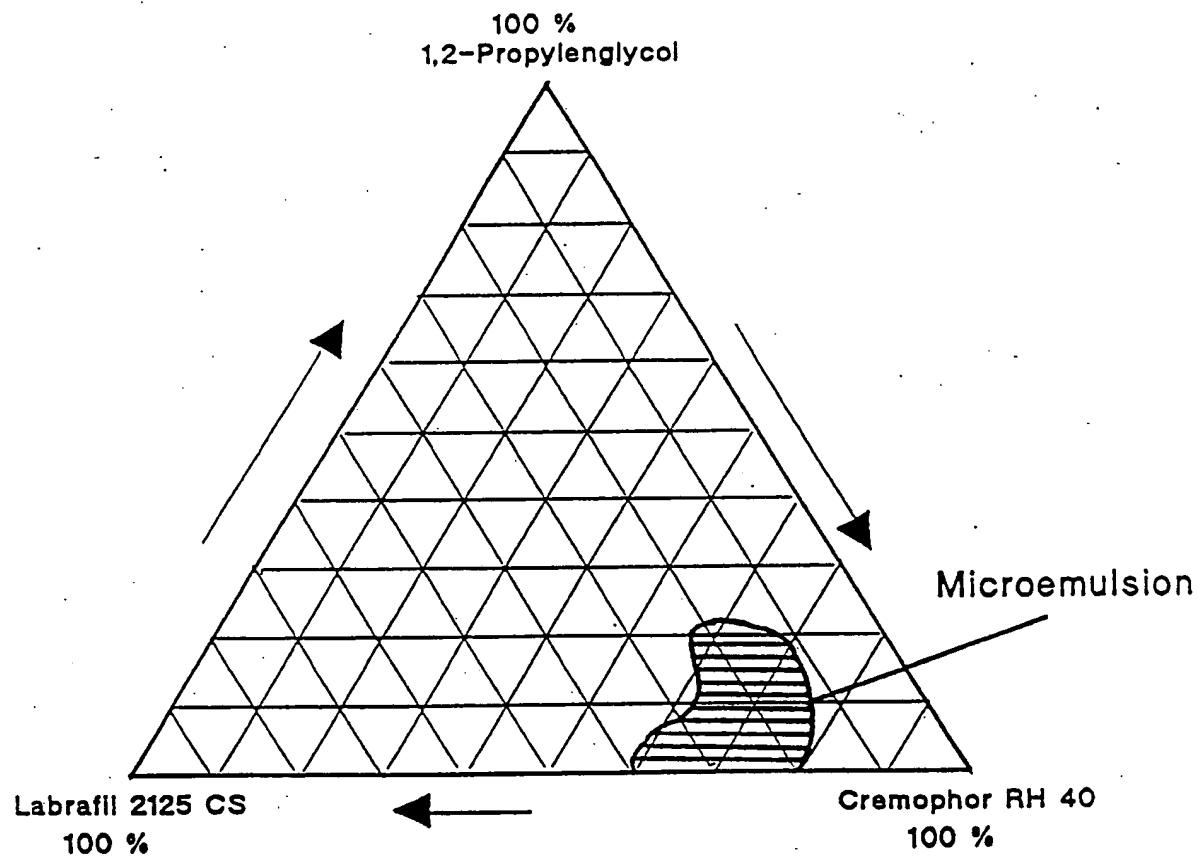


FIGURE 1

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 93/00955

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K37/02; A61K9/107

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	EP,A,0 296 122 (SANDOZ) 21 December 1988 cited in the application see claims see page 34, line 13 - line 50 ---	1-13
Y	GB,A,2 222 770 (SANDOZ) 21 March 1990 cited in the application see claims ---	1-13
Y	GB,A,2 015 339 (SANDOZ) 12 September 1979 see claims see examples -----	1-13

⁶ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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⁸ "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

⁹ "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

¹⁰ "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 25 JUNE 1993	Date of Mailing of this International Search Report 08.07.93
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer SCARPONI U.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300955
SA 73222

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		SE-A-	8903042	11-05-90
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GB-A-2015339	12-09-79	CH-A-	636013	13-05-83
		AT-B-	375828	10-09-84
		AU-B-	528714	12-05-83
		AU-A-	4486279	13-09-79
		BE-A-	874628	05-09-79
		CA-A-	1139667	18-01-83
		DE-A,C	2907460	13-09-79
		FR-A,B	2419072	05-10-79
		JP-C-	1404998	09-10-87
		JP-A-	54132223	15-10-79
		JP-B-	62007891	19-02-87
		NL-A-	7901703	11-09-79
		SE-B-	445174	09-06-86
		SE-A-	7901683	08-09-79
		US-A-	4388307	14-06-83
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